Mediators of Pain and Pain Processing

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Background and Historical Perspective

The mechanisms of pain processing are well researched, but significant anatomic and neurobiological unknowns still exist. The perception of pain by the human body involves complicated interconnections between several different areas of the spinal cord, brainstem, and brain. There are well-defined pathways that assimilate and disseminate noxious input, while other more elusive pathways exist that integrate the body's response to tissue damage and determination of the longevity of the pain experience.

Primary Processing of Pain

Ascending Pain Pathways

Nociception, or the perception of pain, occurs through sensory input from the vast neuronal network known as the somatosensory nervous system (SSNS). The SSNS is not just responsible for nociception as it also senses pressure, light touch, tactile discrimination (e.g., course or smooth), vibration, and body position. The SSNS also codes for graphesthesia, stereognosis, and two-point discrimination. The anatomy of the SSNS is often discussed in terms of first-, second-, and third-order neurons that are responsible for the reception of, integration of, and the coordinated response to the painful stimulus, respectively.

First-order neurons are peripheral pseudo-unipolar neurons that detect pain through specialized nociceptors. A nociceptor is a receptor on a free nerve ending associated with the peripheral branch of the first-order neuron. Pseudo-unipolar neurons have cell bodies in the dorsal root ganglion (DRG) and have only one axon that bifurcates into a peripheral branch that ends in a sensory receptor and a central branch that leaves the DRG and communicates with the spinal cord. The DRG is a structure that is formed by a large cluster of peripheral neuron cell bodies and other cells and neuromatrix (see Fig. 8.1). The DRG is located just distal to the spinal nerve and rootlets and is located just outside of the neuroforamen in most levels.

Receptor Activation

Reception of the nociceptive stimulus involves transduction of the stimulus in the periphery from the initial form of noxious stimulus to a neuronal signal that is transmitted rostrally. This is accomplished through a variety of receptors in the ending of first-order neuron. Membrane proteins such as the transient receptor potential (TRP) family of ion channels are a well-characterized group of specialized nociceptors (Fig. 8.2). TRP receptors respond to noxious, chemical or thermal stimuli, or to changes in pH. The TRP-1 receptor is one that has been identified to be sensitive to capsaicin, to thermal changes as well as pH changes associated with tissue damage. TRP-2 is activated by extreme temperature elevations, and TRP-8 is known to respond to cold stimuli. Other ion channel receptors include SCN9A, a receptor classified as tetrodotoxin-resistant Na2+ channels. Genetic deletion of this receptor is found in those patients who are completely unable to sense pain. Some receptors are known to have purinergic ionotropic binding sites (e.g., adenosine/ATP) that are coupled to Mas-related receptor family that sensitize receptors after tissue damage.

First-Order Neurons

Nociceptive first-order neurons (FONs) (aka peripheral nociceptive afferents, PNA) can be divided into two classes: A-delta ("fast") and C fibers ("slow"). "Fast" pain and "slow" pain is often temporally referred to as the "first wave" and "second wave" of a painful event, respectively. For example, a hammer to thumb event may initially be conveyed as a sharp signal (first wave), but delayed sensations (second wave) may be perceived as a throbbing sensation. A-delta type I neurons respond to fast pain that is well defined and

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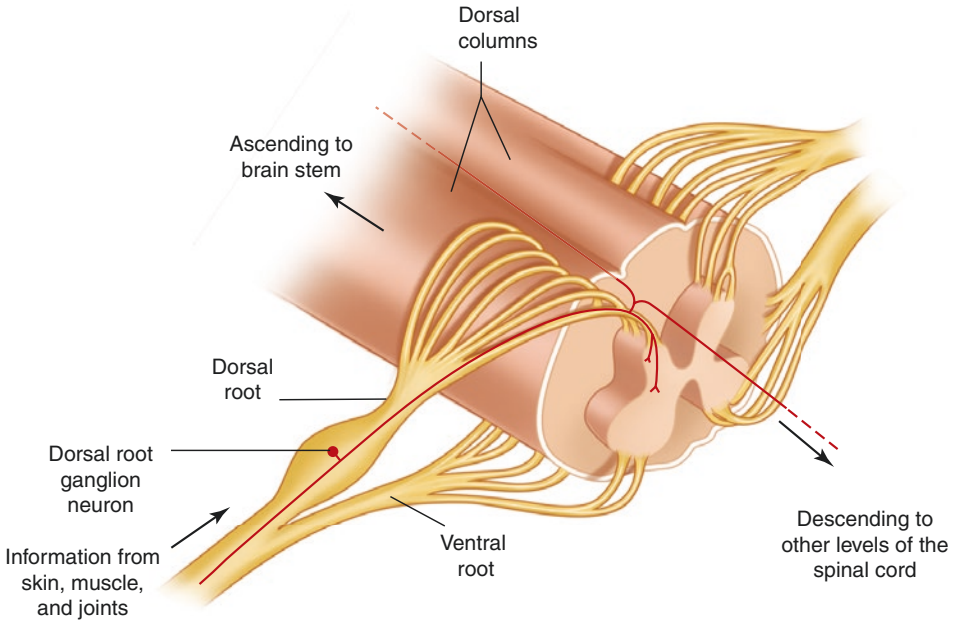

Fig. 8.1 The dorsal root ganglion. The dorsal root ganglion is the collection is unipolar neuron cell bodies. The dorsal root ganglion is responsible for the synthesis of the neuromatrix and associated species responsible for proper function of the neuron

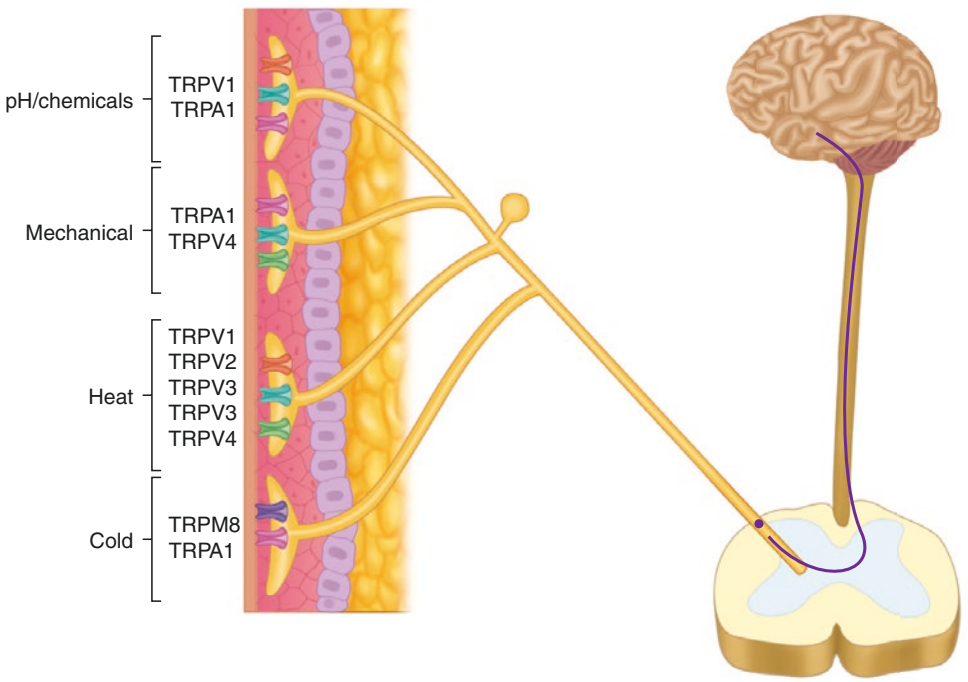

Fig. 8.2 Peripheral nociceptors of the TRPA and TRPV families. There are multiple receptor subtypes associated with one type of stimulus, and signal transduction is relayed to an action potential in the unipolar neuron to the dorsal horn

localized. A-delta-1 neurons are responsive to heat after prolonged or repetitive exposure, but they are initially poor responders to temperature. Initial response to heat is received by type 2 A-delta neurons.

On the contrary, C fibers are neurons that transmit "slow pain" that is not well localized usually as a result of tissue injury. Slow pain can be characterized as a diffuse burning or throbbing sensation. C fibers are responsive to chemical, thermal, and mechanical stimuli although they can have subspecialized roles by containing more than one receptor type. High-threshold receptor C fibers respond to noxious thermal and/or mechanical stimuli (e.g., "polymodal"). Visceral and deeper somatic FONs are exceptional as they can be associated with autonomic activation and associated negative effects.

A-beta fibers are a third type of FON that merits special mention. Under normal conditions they are responsible for mechanical sensation that is not painful. However, A-beta

fibers may be responsible for mechanical allodynia under pathological conditions associated with injury.

Upon activation, FONs transmit the signal to the gray matter of the spinal cord. The area of the spinal cord segment is known as the dorsal horn (DH), whereas the corresponding locations ventrally are referred to the ventral horn (VH). FONs associated with touch, vibration, or limb position synapse in the dorsal columns (DCs) of the spinal cord at specific areas. The gracilis funiculus is the area of the DC that received sensory input from the mid thoracic and caudal body regions, whereas the cuneate funiculus is the target input from the mid thoracic and cephalad structures. These FONs branch into the DH as they unilaterally ascend for the purpose of reflex pain feedback mechanisms.

The rexed lamina (RL) are anatomical layers within the gray matter of the spinal cord, and each layer appears to contain a variety of target cells. Similarly, it is important to understand that each lamina is not exclusive to one cell type as intercommunication between layers occurs. Generally, lamina I receives input from predominantly A-delta and some C fibers in response to noxious stimuli, with some of these specializing in intense temperature (C fiber derived) or both noxious and non-noxious mechanical stimuli. Lamina II (substantia gelatinosa) receives mainly C-fiber input with some A-delta fibers, and it contains a mix of inhibitory and excitatory interneurons mediating both painful and non-painful inputs. Lamina II also receives input from A-beta fibers. Lamina III and IV generally do not mediate painful stimulus input but instead receive a significant amount of input from A-beta FONs, although some A-delta fibers are also present. A-beta fiber input with some A-delta and C fibers synapse in Lamina V. Laminae VII and VIII are not well defined. These likely receive innocuous input. Lamina VII appears unique in that it received input from stimulation from either body side and could be associated with bilateral painful conditions. Lamina X receives input from C fibers, A-delta fibers, and unmyelinated visceral FONs. Laminae II, III, and IV are the only layers that contain non-nociceptive inputs. FONs target either silent neurons that behave in a binary capacity (either on or off) or wide-dynamic range (WDR) neurons that demonstrate a broad capability. WDR neurons respond in a graded response rather than a binary response as above. WDR neurons provide FON stimulation the ability to elicit a divergent response but also receive multiple inputs from a heterogeneous source of both noxious and innocuous FONs, but some also contain wide-dynamic range (WDR) interneurons (lamina IV) or both WDR neurons and nociceptive-specific neurons (lamina II). WDR neurons are predominantly found in laminae IV, V, and VI (see below).

Nociceptive FONs release a wide variety of neurotransmitters (NTs) onto targets in the DH. There are several NTs to include glutamate, substance P, calcitonin gene-related peptide (CGRP), adenosine triphosphate (ATP), nitric oxide (NO), and prostaglandins among others. In terms of classification, PNAs are sometimes viewed in terms of the NT they release. However, PNAs may release one or more than one NT, and the relative quantities may vary based on tissue type, characteristics of initial stimulus (i.e., brief vs. prolonged), or the presence of a pathological condition. Lastly, PNAs may also be grouped into subsets based on their sensitivities to known toxins (i.e., capsaicin).

The response within the spinal cord to PNA activation and transmission is dependent not only on the characteristics of stimulus or type of NT but also on the second messenger systems involved. Second messenger systems are known to be G-protein-mediated intracellular responses that lead to a wide variety of outcomes within the target cell. Second messenger systems may be G-protein-specific stimulatory or inhibitory, leading to activation or inhibition of the intracellular second messenger or an associated ion channel. Similarly, receptors may be associated with a variety of tissue-specific second messenger systems. For example, peptidergic C fibers release the excitatory amino acid glutamine as well as other NTs such as tachykinins, substance P (SP), neurokinin A, and CGRP. Neurokinin A and SP may both activate neurokinin receptors and are associated with the second messenger system phospholipase C (PLC). In contrast, CGRP is associated with the second messenger adenylyl cyclase (AC). Glutamate and EAA aspartate activate glutamate receptors that demonstrate a broad post-activation capability (metabotropic glutamate receptors vs. ion channel receptors AMPA and NMDA). These glutamate receptors of the NMDA subclass are found in abundance in the DH. In addition to glutamate, these receptors require glycine to activate the receptor. This receptor is an ion channel for calcium (Ca2+) permeability of the membrane. Similarly, AMPA glutamate receptors predominantly exist on nociceptive neurons through the spinal cord, and they determine the permeability of Ca2+ at their targets. Generally these receptors have less affinity to glutamate, are kinetically quicker, and transmit sodium ion (Na2+) rather than Ca2+ through their channels. Alternatively, metabotropic glutamate receptors have a number of receptor subtypes and are present throughout SSNS pathways. At the dorsal horn, receptor subtypes mGLU1 and mGLU5 predominate in the transmission of nociceptive input through second messenger systems such as PLC and AC. Others subtypes may act on gene transcription or modify K+ channels.

The PNA-DH synapse is known to demonstrate synaptic plasticity. Synaptic plasticity is known as the ability for neurons to demonstrate autoregulation at the synaptic junction. Synaptic plasticity can occur presynaptically or postsynaptically. Presynaptic modulation can result in the facilitation or inhibition of neurotransmitter release from the axon terminal. For example, presynaptic NMDA receptors at junctions that release EAAs and SP may demonstrate

further presynaptic release of these NTs. In contrast, some presynaptic mGLU receptor subtypes are thought to suppress their own release through inhibitory second messenger systems. Similarly, both postsynaptic and presynaptic facilitation may occur. For example, in some cells SP not only activates NK-type receptors postsynaptically but also may facilitate its own release through presynaptic mechanisms. Ultimately, the effects of different NTs upon target cells depend on the NT, the type of PNA and support cells (glia, interneurons), the wide variety of receptor types as associated local target cells, and associated second messenger systems involved. However, synaptic transmission within the spinal cord is further complicated by the presence of a vast array of target cells to include interneurons and projection neurons.

Second-Order Neurons

Dorsal horn neurons receiving input from PNAs may fall into three broad classifications: silent neurons, wide-dynamic range (WDR) neurons, and non-nociceptive neurons. These neurons communicate within each segment, among segments, or at supraspinal levels. Projection neurons (PN) are DH neurons that communicate with supraspinal targets and are found predominantly in lamina I, V, and VI. Interneurons (IN) communicate locally and are responsible for local modulation and integration of signals from PNAs. These INs are generous in lamina II, and they may be excitatory or inhibitory, but some IN function in both capacities.

Excitatory interneurons (EIN) in lamina II may indirectly facilitate transmission of PNAs through activation of PN in lamina I when targeted by PNAs. Similarly, EINs targeted by PNAs can also facilitate transmission of PNAs by reflexively stimulating the terminals of PNAs in a feedback loop fashion. EINs from lamina II may influence PNs from deeper lamina V through dendrites from these layers that reach to lamina II. In particular, A-beta fibers project to lamina V as do some C fibers. EIN may play a role of intercommunication between these fibers in some disease states that require A-beta and C fiber facilitation. EAAs involved may include SP, glutamate, and vasoactive intestinal peptide (VIP).

Inhibitory interneurons (IIN) act to suppress the activity of their target cells. These antinociceptive INNs utilize a wide variety of neurotransmitters (NT) that have receptors coupled to ion channels to hyperpolarize a target cell or work by G-protein-coupled second messenger systems in a cascade-like fashion to induce suppression. These receptors (with corresponding neurotransmitters) include predominantly muscarinic cholinergic (acetylcholine), opioidergic (endogenous opiate peptides, enkephalins, dynorphin), and GABAergic (gamma-aminobutyric acid [GABA]). The IIN cohabitate with antinociceptive NTs (e.g., substance P) or pro-nociceptive (e.g., nitrous oxide). This cohabitation of NTs complicates any suggestion that INs are mutually exclusive to one role or another. Lastly, IINs act presynaptically on target PNA or postsynaptically on target PN. In addition, PNA cells also directly target IINs that reciprocate stimulation in an antinociceptive feedback loop.

Other support cells exist in and around the dorsal horn and throughout the CNS. Glial cells and immunocompetent microglia secrete local chemical mediators and play an important role in the modulation of pain signals in the presence of central or peripheral tissue damage.

Glial cells are known to be support cells for local homeostasis within the central nervous system (CNS). Not only do they possess channels for Ca2+, the cell membrane hosts a variety of receptors to NTs that are involved in the transmission of pain. Glial cells receive synaptic transmission (glutamate) promoting the release of chemical mediators (NO, prostaglandins [PGs], adenosine triphosphate [ATP], cytokines) that facilitate nociception in the presence of central or peripheral inflammation. Cytokines appear to have dual roles, however. In some cases (IL-6) cytokines may induce or facilitate allodynia and hyperalgesia, while other cytokines (IL-1beta) may promote inhibition of nociceptive signals in the dorsal horn or inhibit long-term potentiation in central sensitization.

Projection neurons (PN), as opposed to interneurons, by definition leave their segment of origin. These sensory pathways may be organized into monosynaptic pathways (MSP) and polysynaptic pathways (PSP). The former group is composed of PN that synapse directly onto specific central targets. Known MSP include the spinothalamic tract (STT), spinomesencephalic tract (SMT) (spinoparabrachial tract [SPT]), spinohypothalamic tract (SHT), and the spinoreticular tract (SRT). Polysynaptic pathways include the spinocervical pathway (SCP), the postsynaptic dorsal column pathway (PDCP), and second-order neurons that arise from connections in higher centers such as the lateral cervical nuclei (SCP) and the cuneate and gracile nuclei (PDCP) in the medulla. These pathways are predominantly non-nociceptive with some exception.

The main purpose of ascending pathways is to transmit nociceptive information to higher centers in the brain from the skin, musculoskeletal system, and the viscera. A wide range of pathways and NTs exist to accomplish this. It is somewhat helpful to understand ascending pathways by discussing them in the context of regions of the spinal cord rather than as independent pathways. The prevailing concept to understand the organization and function of afferent nociceptive transmission is that it is dynamic and multimodal and is determined by the physiological or pathological circumstances present (Fig. 8.3).

The PSDCP is located in the dorsal midline of the spinal cord. These dorsal columns (dorsal funiculi) predominantly contain fibers that are non-nociceptive (position, vibratory). However, PSDCP may receive input from other known pain

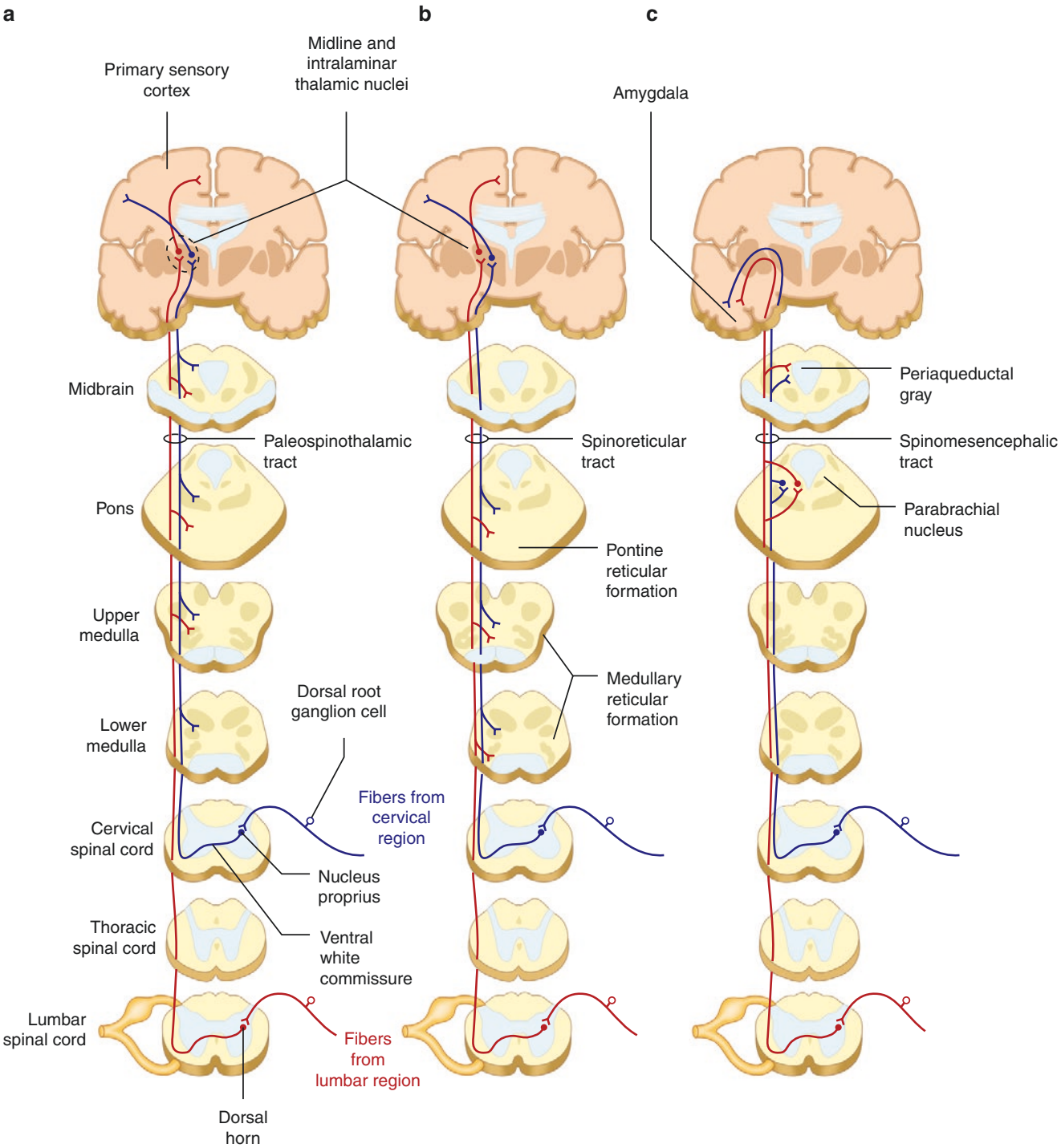

Fig. 8.3 Ascending pathways. While most non-nociceptive information is relayed through the dorsal horns, nociceptive stimuli are relayed to the ventrolateral horn associated with some ascending tracts. Unipolar neurons transmitting nociceptive information synapse with secondary neurons that decussate to the ventrolateral columns. Ascending tracts are polysynaptic. Branches to structures within the brainstem en route to the primary somatosensory cortex provide integration of the response to nociceptive stimuli

pathways such as the spinothalamic, spinomesencephalic/spinoparabrachial, and spinocervical pathways found in the dorsolateral funiculus (DLF). In particular, neurons from lamina I associated with the STT connect to a dorsal spinothalamic tract in addition to its known tract in the ventrolateral funiculus. Therefore, due to the polysynaptic nature of the PSDCP, it may be strongly involved in the pathological state of mechanical allodynia.

The monosynaptic pathways project contralaterally whereby PNAs synapse on PNs that either decussate immediately or at direct adjacent levels to the ventrolateral funiculus. The ventrolateral funiculus (VLF) is organized such that fibers emanating most cephalad are medial whereas fibers originating in the caudal regions are more medial. The STT and SHT ascend predominantly in the VLF, but some PNs are also included in the DLF as well. However, the SHT is unique in the sense that upon reaching the hypothalamus, PNs ascend and decussate once again to contralateral targets in the diencephalon lending it to impose transmission at targets bilaterally. The SRT and SMT largely use the VLF, but the SRT also contributes PNs to the DLF that remain ipsilaterally, while the SMT ascends on the contralateral side. The SPT appears to traverse the spinal cord dorsally in the contralateral DLF as well.

The overall experience of pain is determined by the interaction between the two categories of ascending pathways. The sensory-discriminative pathways are responsible for the identification of a painful stimulus and encoding of the location, intensity, duration, quality, duration, etc. The affective-cognitive pathways are responsible for the psychological aspect of the pain and the role of mood, memory, toleration, and coping with painful stimuli. No single pathway likely predominates, and the overall experience of pain is dependent on the character of signal input to, and integration within, the supraspinal targets.

Third-Order Neurons

The concept of a single pathway for the transmission of pain stimuli to the brain is likely an oversimplification given the known complexity of the lamina and corresponding ipsilateral and contralateral trajectories of their PNs. However, the interrelationship of these tracts appears to begin within the nuclei of the thalamus.

The thalamus serves to communicate to the limbic system and integrates the emotional experience of pain with the sensory-discriminative component. The thalamus is a bilateral structure with the left and right sides appearing to be mirror images. The thalamus is an organized cluster of nuclei that serve to receive, integrate, and relay noxious input to the cortex and limbic system.

The ventroposterolateral (VPL), ventroposterior medial (VPM), and ventroposterior inferior (VPI) nuclei are key nuclei in the receipt and processing of noxious stimuli. The ventral STT preferentially innervates the VPL and VPM nuclei, while the dorsal STT appears to preferentially innervate the VPI nucleus. The VPL and VPM neurons appear to have small receptor field and therefore appear to be predominantly involved in the sensory-discriminative aspect of pain. The posterior thalamus to include the posterior division of the ventromedial nucleus (VMpo), the pulvinar and posterior nucleus also receives input from the dorsal STT, and it is involved with the integration of nociceptive and thermal stimuli. Lastly, the ventral caudal position of the medial thalamus receives dorsal STT input and communicates to the striatum among others and may be involved in the escape mechanism from painful stimuli. The VPI, VMpo, and the ventral caudal medial thalamus may also integrate the attention to, and understanding of, emotional response to pain.

The neurotransmitters responsible for communication within the thalamic nociceptive and WDR neurons are not clear, but some trends conserved the lamina. EAAs play an excitatory role within the VPL and VPM nuclei where their responses are mediated through NMDA and metabotropic glutamate receptors, and their cortical projections appear to be similar. A significant proportion of the thalamus also consists of GABAergic IINs. The IINs in the thalamus subdue excitatory output. Dysfunction of this inhibitory mechanism may lead to unopposed pro-nociception. This may be a core mechanism in chronic pathological pain.

Thalamic projection neurons (TPNs) to higher centers appear to be arranged into sensory-discriminative pathways and affective-cognitive pathways. The somatosensory cortex I/II, inferior and anterior parietal cortex, the insular cortex, the anterior cingulate, and prefrontal cortex all appear to be target sites for TPNs. The VPL and VPM provide a large input to the somatosensory cortex. The VPI provides a large input to the secondary somatosensory cortex. While TPNs from the VPL and VML widely innervate the primary somatosensory cortex, local WDR and central nociceptive-specific neurons within this cortex possess small contralateral receptive fields. Small fields provide the ability to narrow the location and intensity of painful input, and repetitive stimulation of WDR neurons may lead to central sensitization. While some TPNs from the posterior thalamic nucleus also project to the primary somatosensory cortex, the secondary somatosensory cortex received input predominantly from VPI and posterior nucleus. There are studies that show that experience pain is present even in the presence of a lesion within the STT-VPL-primary somatosensory cortex pathway; the acceptance of a single ascending pain pathway is no longer reasonable.

There are other cortical regions involved in the interpretation of pain. While the primary cortex receives very specific encoding information, other areas such as the secondary cortex, inferior parietal cortex, or anterior cingulate gyrus are more specific to the emotional component of the pain. Input to these areas and the associated response are dependent on the thalamic nuclei from which they receive input.

The limbic system is composed of the limbic lobe (the annular area of the cortex), the amygdala, and the hippocampal formation. The limbic system is responsible for primal functions of the brain to include, but limited to, activation of "fight or flight" responses and emotional states. Since the limbic system is composed of several CNS structures, their

interrelationship and activation patterns through WDR and nociceptive neuron input determine the complicated emotional/behavioral response to painful stimuli.

The limbic system receives input both directly and indirectly. Indirectly, areas of the cortex that are part of ascending tracts also relay information back to the thalamus and to the limbic system in a reciprocal manner to affect cognition and mood. Direct input to the limbic system occurs both from the PBN and the periaqueductal gray (PAG) as it is relayed via the SMT. The cingulate gyrus of the limbic lobe and the insular cortex receive significant nociceptive input, whereas insula receives input directly from the VPM nucleus and is associated with the autonomic component of pain.

The ascending integration of pain processing consists of several pathways that cannot be considered mutually exclusive. The ventral lateral fasciculus and ventral STT relay information to the VPL area of the thalamus and are integral in the interpretive precision of the painful stimulus (location, intensity, etc.). The emotional experience of the painful stimulus appears to be mediated through the dorsal STT and the PSDCP as ascending nociception reaches the VPI and VMpo and relayed to the cortex and limbic system. Similarly, the PAG, amygdala, and PBN among other areas receive direct input from areas other than the ventral STT and influence or be influenced by the emotional component of pain as seen in clinical scenarios where pain leads to depression or anxiety, and the presence of these mood states worsens clinical symptoms of pain.

Descending Pathways

Descending modulation of nociception is thought to occur in the dorsal horn rexed laminae. Descending influence can lead to facilitation or inhibition of ascending pain pathways. Descending fibers arise from many sites in the supraspinal compartment and project fibers to the dorsal horn. Similarly, both DI and DF fibers may have common sites of origin. As with ascending pathways, DI and DF exert their influence and are dependent not only on the type of neurotransmitter but also milieu of receptor phenotypes and postsynaptic target cell types.

The connectivity of descending pathways is very complex. In general, some pathways may originate from one supraspinal source but traverse different areas of the spinal cord as they descend and may have entirely divergent functions (e.g., DI and DF). Neurons may descend within the spinal cord through the dorsolateral or ventrolateral funiculi. Whether inhibition or facilitation of a pain signal occurs may depend on whether the neuron directly synapses on the terminal of the PNA or mediates its effects through IINs. For example, DI pathways may act directly onto the PNA to release inhibitory NTs onto the terminal itself thereby decreasing synaptic transmission by the PNA onto the PN. Similarly, the DI pathways may release excitatory NTs directly onto an IIN whereby activation of this IIN leads to synaptic depression at the PNA-PN synapse either pre- or postsynaptically. Furthermore, DF may occur in similar mechanisms by either facilitating PNA synaptic transmission by direct presynaptic potentiation or by activation of EINs. During baseline function of the body, the counterbalance between DI and DF prevents the exaggeration of signals received from the periphery. However, under pathological conditions, this balance may be disrupted.

Several supraspinal regions participate in the descending modulation of nociception. These include the hypothalamus, parabrachial nucleus (PBN), nucleus tractus solitarius (NTS), rostroventromedial medulla (RVM), nucleus raphe magnus (NRM), dorsal reticular nucleus of the medulla (DRN), periaqueductal gray (PAG), and the cerebral cortex.

The hypothalamus holds a significant role in the autonomic response to and cognition of pain. Afferent pathways heavily target the hypothalamus. However, it exerts descending indirectly through intermediaries and not directly onto the dorsal horn. These structures include the NTS, PAG, RVM, and the limbic system, and they are integrated with the hypothalamus to coordinate both affective and cognitive aspects to painful stimuli. Similarly, the amalgamation nuclei and "centers" that compose this structure differentiate themselves through distinct targets and NT pathways. For instance, the medial preoptic nucleus of the hypothalamus is closely connected to the PAG and may suppress nociception through autonomic activation, while other parts of the hypothalamus (e.g., lateral hypothalamus) may activate descending noradrenergic pathways affecting the DH cells.

As described above, the PBN is known to play a role of pain cognition and emotion as well, and it functions similar to the hypothalamus in response to predominantly visceral nociceptive input. The PBN is known to mediate its effects by projecting to structures similar to the hypothalamus, and activation of the PBN may lead to suppression of nociception in the superficial layers of the DH.

The PBN shares similarity with the NTS in the mediation of visceral pain. The NTS is responsive to visceral afferents largely through input from the vagus nerve but also via DH fibers. The PBN and NTS are both heavily interlinked with limbic structures, the hypothalamus, and the cortex. The NTS ultimately projects not only to the PAG but also mediates nociception directly in the DH or through other adrenergic and serotonergic nuclei-associated projections in the modulation of nociception.

The RVM houses several nuclei associated with descending modulation of nociception and provides a signal conduit for input from other supraspinal areas. The heterogeneity of this structure lends itself to roles of both DF and DI, and this dual ability is underscored by the diverse structures that

provide input to the RVM (e.g., PBN, NTS). The RVM nuclei are a major contributory center to the mediation of pain associated with tissue and nerve injury.

The DRN of the medulla receives both somatic and visceral input. The DRN appears to be involved in the mediation of pain through descending pathways that terminate in the DH. Similarly, the DRN itself is targeted by DH afferents. Communication between targets in the SC and the DRN appears to mediate hyperalgesia, and in response to tissue damage, the DRN is activated to provide a response that leads to antinociceptive analgesia.

The PAG is also strongly associated with the limbic system, hypothalamus, NTS, and PBN in the mediation of pain and emotion (Fig. 8.4). In addition to supraspinal structures, the PAG also receives direct input from the periphery via PNs. The PAG houses receptors for a variety of neurotransmitters, to include opioid agonists and cannabinoids among a variety of others. The PAG appears to be under tonic inhibition from IINs, and resolution of tonic inhibition by, for example, mu-opioid agonists may lead to the facilitation of descending inhibition through at least in part the descending noradrenergic system. Therefore, the PAG serves as what appears to be a central clearinghouse for the integration of multiple signals to include influence by structures that may or may not provide descending input (i.e., amygdala) (See Fig. 8.5).

Lastly, descending modulation of nociception appears to be mediated not just through subcortical structures (i.e., PAG) but also through a lesser-known pathway involving the dorsal column nucleus. Descending pathways exit from the cortex to the dorsal column nucleus and may play a significant role in the facilitation of neuropathic and visceral pain. Similarly, some cortical areas appear to project to the RVM to include the NRM as well as to the PAG, thereby promoting influence on the DH. Thus, cortical areas appear to provide both direct and indirect influence on nociception through either monosynaptic or polysynaptic means.

As previously alluded, there are multiple descending pathways and their associated neurotransmitters. Norepinephrine (NE, aka *noradrenaline (NA), noradrenergic*) and serotonin (5-HT, *serotonergic*) are well researched, but other pathways exist to include dopamine (DA), acetylcholine (ACh, *cholinergic*), endorphins, adenosine, and glutamate, to name a few. However, the target receptors and

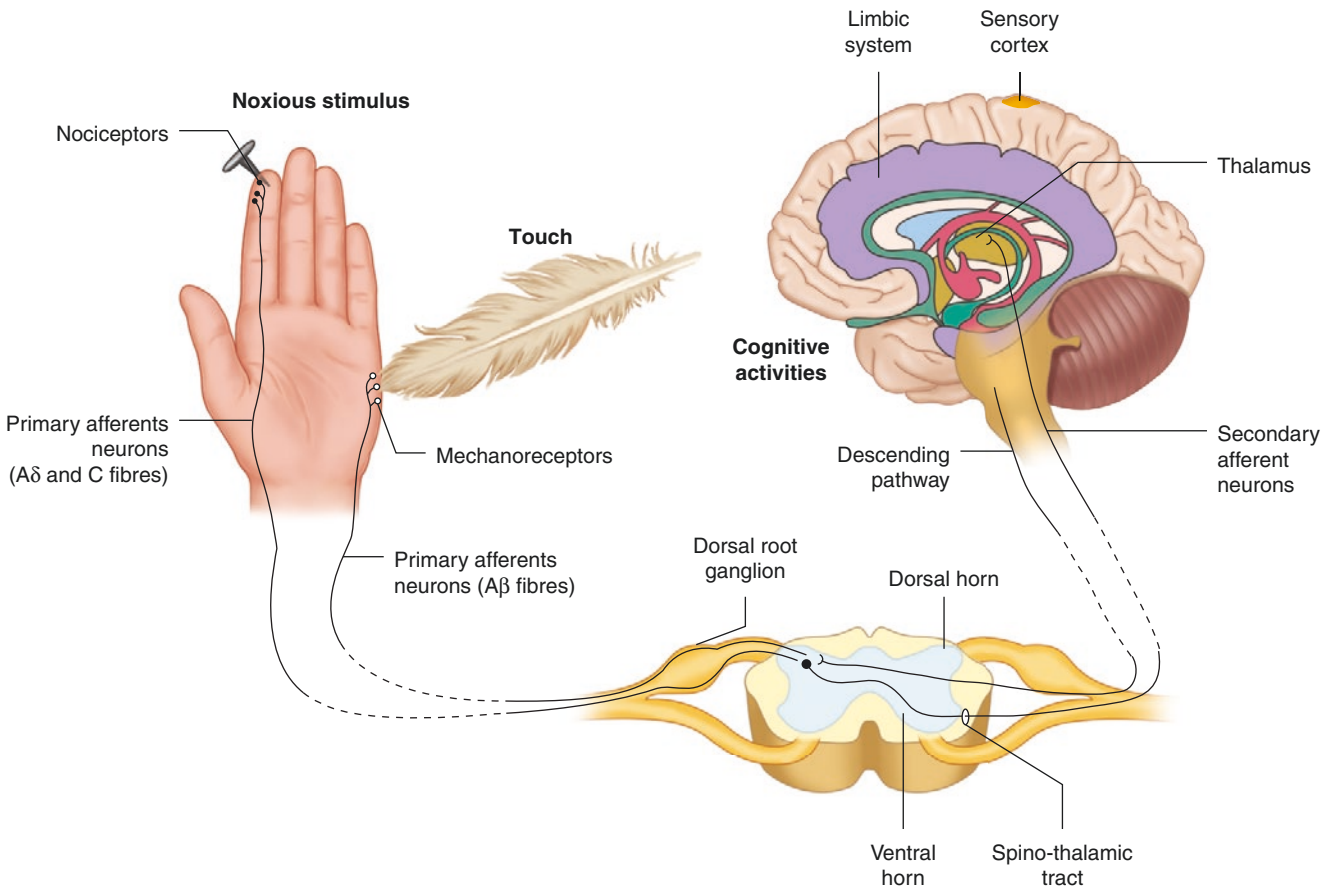

Fig. 8.4 Cognitive-affective pathways. Complicated integration of ascending pathways with the thalamus and limbic system is an important determinant of the outward display of pain. The cognitive-affective dimension of pain may further determine the plasticity of the pain response

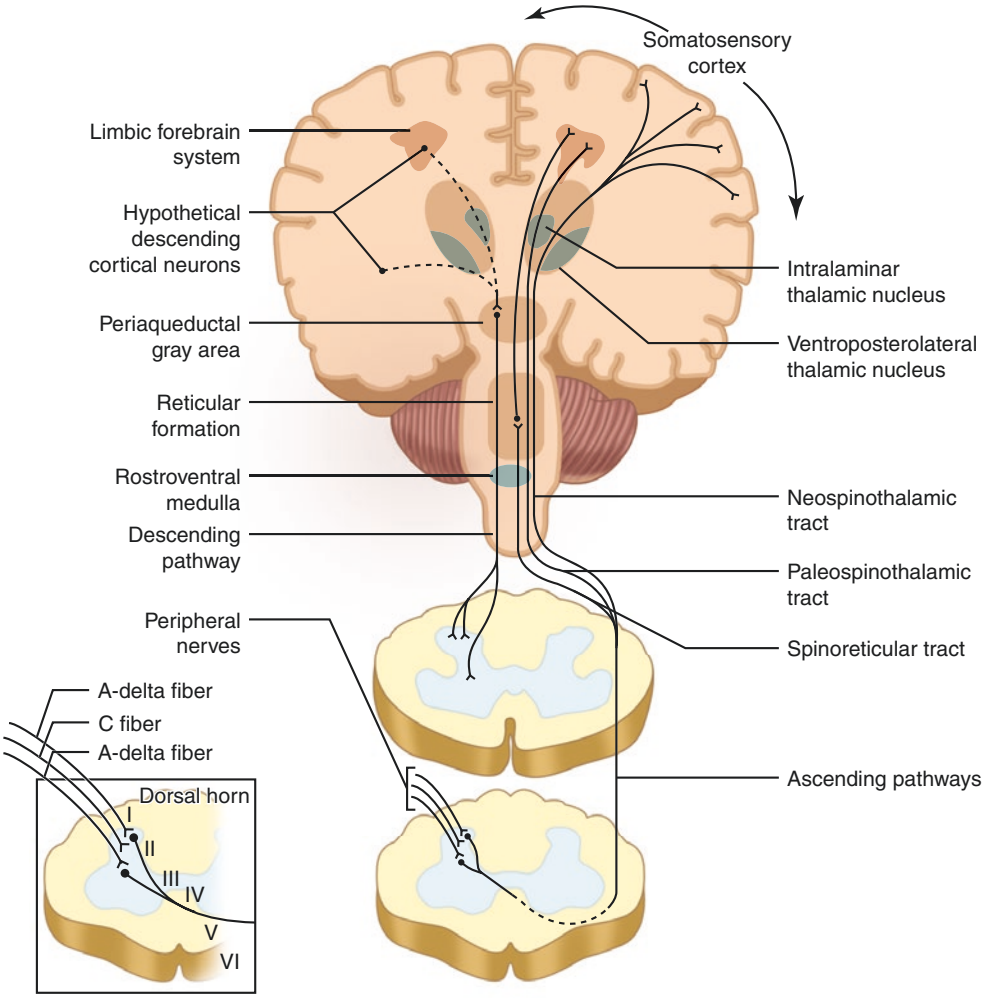

Fig. 8.5 Ascending pathways and descending pathways. Both ascending nociception and non-nociceptive input are relayed centrally through the medulla to the thalamus, limbic system, and the sensory cortex. Descending controls exert their influence through potential facilitation or inhibition through common structure such as the periaqueductal gray area and the thalamus. Cortical descending control mechanisms also may exist

associated second messenger systems provide NTs with diverse and often divergent responses under normal or pathological conditions.

The descending noradrenergic pathway is a well-studied pathway, and it is well known to modulate nociception under normal conditions as well as stress-induced and pathological states. Centers in the medulla and pons may provide descending input through the intermediolateral columns and ventral horn. Medullary nuclei and areas of the locus coeruleus are known sources of these descending NA pathways. These structures are under tonic inhibition from gamma-aminobutyric acid (GABA)-related pathways, a site of possible antinociception for cannabinoids and opioids. Opioid activation in the PAG may also lead to the increased activity of NA by release of inhibitory influence.

The NA descending pathway role is likely determined by circumstances associated with stimulus input. The influence of the NA descending pathway is subtle under normal conditions. However, with increasing stimulus intensity, the role of this pathway changes at least in the acute phase of nociception. Further painful stimulus involving injury or inflammation may lead to recruitment of more neurons of the NA pathway and segue to bridge nociception and the cardiovascular system response to pain. The NA pathway is also known to exhibit influence on the RVM, the heterogeneity of which may influence both DI and DF.

The DI effect of NA is mediated likely through the role of the alpha-adrenoceptor. This receptor is present in significant quantities in the DH as well as in sufficient amounts in the dorsal root ganglion (DRG). NA provides significant suppression of nociception through presynaptic inhibition of PNA NT release in the DH although the extent varies upon location in the CNS. The alpha-2 receptor targets in the rexed laminae lead to target cell inhibition through G-protein mediation target cell hyperpolarization (increased K+ influx) and inhibition of AC. Under certain conditions, volume transmission, or bulk flow of large quantities of NA, can also play a role in mass receptor activation. Furthermore, NA is co-localized with other NTs such as ACh, GABA, adenosine, and others. Although NA promotes DI by the specific activation of alpha-2 adrenoreceptors, there is a preponderance of evidence to suggest that NA more broadly

modulates nociception and the individual roles of the other transmitters directly and indirectly. Lastly, the role of the alpha-1 adrenoreceptor is important in the context of pronociception. While the role of the alpha-2 is clear, the alpha-1 receptor appears to facilitate pain signaling most predominantly in the intermediolateral columns and VH. Similarly, these receptors are present at PNA terminals and facilitate their neurotransmission. However, this pronociceptive influence may also be dose dependent, and this may pose a quandary for alpha-2 receptor analgesics through crossover binding.

The serotonergic pathways within the spinal cord appear to entirely originate from the supraspinal structures. The preponderance of 5-HT in the dorsal spinal cord appears to arise from the RVM and the NRM. Similarly, a smaller proportion of 5-HT fibers may also come from the DRN, a structure that affects the thalamus, hippocampus, and trigeminal nucleus among others. These 5-HT neurons descend to the DH and synapse in the superficial and deep DH in abundance, and they may affect their target PNAs or PNs either by ININs or by volume transmission. There is also pronounced input by 5-HT neurons into the intermediolateral cell columns and ventral horn. These areas receive input from 5-HT projections from the nucleus raphe pallidus among others.

Serotonergic pathways appear to be affected by both acute and chronic pain. In fact these pathways appear to play a role in stress-induced analgesia, and blockade of 5-HT pathways reduces this response. However, this response is also decreased in the presence of peripheral afferent damage. Furthermore, some studies suggest that there is a dual role whereby the serotonergic pathways are involved in both DI and DF, as receptor-specific responses and receptor location are the determinants of this response. This duality appears to depend at least in part on stimulus parameters, with high-frequency and low-frequency stimulation of the RVM leading to DI and DF, respectively. These cells within the RVM are not associated with supraspinal morphine-mediated descending pathways of DF "ON" cells (stimulated by pain, inhibited by opioids) or DI "OFF" cells (stimulated by opioids, deactivated by pain) through central or systemic administration of morphine. However, kappa-opioid receptors are known to mediate the serotonergic response to nociception in the RVM. Kappa receptors are known to directly inhibit primary serotonergic cells, and these cells are also indirectly inhibited by activation of secondary GABAergic cells. Mu- and delta-opioid receptor activation disinhibits these secondary cells, and kappa receptors on these secondary cells lead to disinhibition of GABAergic inhibition (e.g., facilitation) leading to serotonergic DI. Thus, central opioidergic pathways may indirectly mediate descending serotonergic pathways in the DH through a diversity of opioid receptor subtypes. Similarly, there is a variety of other pathways that, as to be discussed later, lead to modulation of the 5-HT pathways. These include beta-endorphins, prostaglandins, and acetylcholine among others.

The dual role of the serotonin pathway in the mediation of pain can be attributed not only to the variety of receptors that bind 5-HT but also to the second messenger system that results from receptor activation. Modalities of control by descending serotonergic pathways include action on neurons of the superficial and deep layers of the DH and associated transmitter release, on the target cell resting state or activation by PNA input, and on the influence of pro-nociceptive NTs and influence upon wide-dynamic range neurons or individual PNAs or interneurons. The temporal pattern of the nociceptive input may also determine the role of 5-HT in the overall perception or prolonged perception of pain with some evidence to point to its poor role in antinociception in the spinal cord in the presence of prolonged neuropathic pain and the depletion of 5-HT in the spinal cord leading to attenuation of pain transmission. Nonetheless, receptor subtype appears to dictate the overall role of 5-HT in nociception. The receptor 5-HT1A is present in significant concentration in the DH and suppresses neuronal firing through the facilitation of K+ current and inhibition of Ca2+ currents. The 5-HT1A receptor appears to mediate hyperalgesia likely through the activation of IINs on PNs in the DH not on PNA terminals. The 5-HTA1 receptor may also play a role in antinociception through direct action on some PNA terminals or through supraspinal pathways emanating from the opioidergic pathways associated with the PAG. Similarly, 5-HT1A may inhibit IINs that suppress NA transmission or presynaptic feedback on their own facilitation of IINs' action on descending NA pathways from the NRM and others. The 5-HT1B receptor is also known to facilitate K+ currents and is found throughout the DH. The 5-HT1B promotes antinociception by negative feedback loop autoreceptors as serotonergic on serotonergic terminals. Similarly, 5-HT1B receptors also appear to medicate antinociception through reduction in the release of CGRP and SP, with 5-HT1D predominant in the cerebral blood vessels. Receptors 5-HT1B, 5-HT1D, and 5-HT1F appear to mediate antinociception in the presence of migraine headache. The 5-HT2 receptor class contains three subtypes with evidence demonstrating that at least 5-HT2A and 5-HT2C are pro-nociceptive in the DH. The receptor 5-HT2A appears to be associated with facilitation of central sensitization at PNA terminals but may also have a role in antinociception through IIN pathways. The 5-HT3 receptor is also an ion channel. It is found in abundance in the superficial laminae. This receptor is known to play an excitatory role in the facilitation of inflammatory pain transmission through modulation of central terminals on PNAs. However, 5-HT3 may also be antinociceptive as well similar to 5-HT2A through an IIN process, but this may include co-localization with other central NT-mediated processes. 5-HT3 receptor may also mediate pain from visceral origin through local

mechanisms mediated through vagal afferents. Other serotonergic receptor classes include 5-HT4, 5-HT5, 5-HT6, and 5-HT7. 5-HT4 receptors appear to be related to pro-nociception as mediated through C fiber PNAs. The 5-HT5A receptor appears to mirror the role of 5-HT1A with a heavy correlation with cerebral structures associated with descending NA pathways. The role of the remaining subclasses of 5-HT receptors although present in the DH (5-HT5, 5-HT6, and 5-HT7) is not well defined.

The dopaminergic pathway appears to play a role in the descending modulation of nociception, but it is much less researched. Origins of DA in the nervous system predominantly include the substantia nigra, the paraventricular nucleus of the hypothalamus, and the A11 region of the hypothalamus. DA receptors are organized into the D1 and D2 receptor families with D1 receptors representing the abundance in the spinal cord. Agonist studies appear to represent that D2 receptors mediate antinociception while D1 receptors are the antithesis. No clear mechanism is known to regulate the descending influence of DA in the CNS, but some studies suggest the roles of the PAG. The A11 regions of the hypothalamus appear to reduce the behavioral response to pain, while D2 receptors on target PNAs or PNs in various rexed laminae reduce their excitatory output.

Other Mediators of Pain Processing: Histamine, Endogenous Opioid Peptides, Nitric Oxide, Cannabinoids, and Other Neuropeptides

Several other transmitters exist in the mediation and transmission of pain processing. These transmitters play an important role not only at the level of the DH but also throughout known pathways involved in DI and DF. As with many species involved in neurotransmission, the mechanisms may be facilitatory or inhibitory, and this is dependent on the receptor subtype and the corresponding second messenger system in place. Furthermore, nociception under normal states and pathological conditions play an important role.

Histamine and its associated receptors are known to be present in the CNS whereby histamine is synthesized by cells in the hypothalamus. These cells project to other areas of the brain and brainstem whereby they exert their effects in a receptor-dependent manner. The histamine receptors are known as H1, H2, H3, and H4 whereby H1 and H2 are known to be excitatory and H3 mediates an inhibitory pathways. In the DH PNA terminals, histamine appears to lead to a pro-nociceptive response with peripheral nerve injury leading to expression of histamine receptors. Histamine appears to exhibit differentiating effects on the serotonergic and noradrenergic pathways in the CNS with the response once again dependent on receptor subtype and location. H2 receptors on the average appear to facilitate DI (possibly in association with opioidergic mechanisms of the PAG) whereby H1 receptors appear to promote nociception. In the DH, H3 receptors at least in part appear to mediate pro-nociception through inhibition of presynaptic NT release in a negative feedback manner. Centrally, activation of H3 autoreceptors reduces overall histamine load and promotion of nociception.

Endogenous opioid peptides (EOPs) are a family of peptide with several known receptors in the CNS. These receptors include mu-, delta-, and kappa-opioid receptors. These peptides are cleaved from parent molecules into biologically active substances and byproducts of yet to be determined significance.

Enkephalins (ENK) are a family of peptides to include met- and leu-enkephalin, and these are cleaved from the parent pre-pro-enkephalin. Globally, these substances are known to promote DI either through direct receptor activation or potentiation of other descending pathways that mediate DI. As with the other EOPs, activation of encephalin receptors leads to antinociception through the promotion of K+ currents and the suppression of C2+ currents through negative G-protein mediation of adenylyl cyclase. Cells containing enkephalins are found in significant quantities of the PAG, and there are significant populations of ENK receptors associated with IINs of the DH.

Dynorphins (DYN) are another group of EOPs, and they are formed from the cleavage of pre-pro-dynorphin. DYN is unique to the class of EOPs in that it may play both pro- and antinociceptive roles. Kappa-opioid receptors are known to mediate the antinociceptive mechanisms of DYN both centrally and in the DH through IINs. However, in the DH, DYN can promote nociception through non-Kappa-mediated mechanisms (i.e., NMDA receptors) or interfere with the actions of DI pathways. Centrally, DYN mediates DI through both kappa receptor-mediated pathways in the PAG and amygdala, but in other supraspinal structures, DYN may potentiate DF or interfere with DI pathways. The antinociceptive role of DYN has to be postulated to, at least, in part, be responsible for hyperalgesia and tolerance associated with clinical opioid therapy.

Endorphins are found in several areas of the brain important in descending modulation to include several aforementioned structures such as the medullary nuclei, PAG, and amygdala. Similarly, endomorphin-2 is found in significant quantities in the DH among particular local networks. Mu receptors are known to mediate their intense analgesic effect.

Pro-opiomelanocortin (POMC) is a large protein that is precursor to beta-endorphin and a group of other products collectively referred to as melanocortins. Beta-endorphin is found in cell bodies of some hypothalamic cells, NTS, and within the DH DRG. Within the hypothalamus, these neurons project to the PAG to provide significant input and lead to mu-opioid receptor-mediated DI as well as in part DI medi-

ated through descending noradrenergic pathways. The role for descending NTS tracts as well as local beta-endorphin-containing cells in the DH and receptors in the DRG is not clear although the role may be inferred as antinociceptive.

Melanocortins are the second known group of products of POMC cleavage, and they include various subtypes of melanocyte-stimulating hormone and adrenocorticotrophin-releasing hormone. Although several receptors have been identified, there is relatively little known of their bioactivity sans the MC4 receptor. The mechanism of melanocortins as mediated through the MC4 receptor appears to be AC-mediated facilitation and pro-nociception. This receptor is produced by cells that do not produce POMC and coexists in the proximity of POMC-mediated antinociceptive receptors. MC4-containing cells are found throughout the PAG, medullary nuclei and NTS, locus coeruleus, and the DH. Activation of the MC4 receptor is thought to attenuate endogenous analgesic mechanisms and promote allodynia.

Nociceptin (aka orphaninFQ) and nociceptin originate from the same precursor polypeptide. OrphaninFQ is an endogenous opioid formed from a pre-pro-peptide that works through its receptor ORL1 that is widely found throughout the CNS. The receptor is homologous to known other EOP receptors, but receptor binding to orphaninFQ results in the mediation of nociception antithesis to known opioidergic mechanisms in spite of documented homologous neurochemistry. OrphaninFQ is found in the PAG and RVM as well as sites in the DH laminae. In the DH, orphaninFQ may act in a pro-nociceptive or antinociceptive dose-dependent manner either by direct action at the PNA terminal or through an intermediary mechanism (i.e., IINs). However, orphaninFQ modulates a diffuse inhibitory effect on DI mechanisms with possible influence on both opioidergic and non-opioidergic pathways. Nocistatin is a peptide product of the parent protein that gives rise to the orphaninFQ molecule. Nocistatin appears to work through different receptors, and its action spinally and in higher centers antagonizes those of orphaninFQ by unknown mechanisms of action.

Galanin (GAL) is a neuropeptide known to exert its influence through three known receptors aptly named GAL-1, GAL-2, and GAL-3. The neuropeptide GAL is known to exhibit a duality of mechanisms remaining in common theme to other species discussed, and this duality is determined by receptor subtype. GAL is found both in the supraspinal and spinal compartments, and it plays a role in both resting and pathological states. In the brain, GAL is found in neurons in the PAG, PBN, NTS, and locus coeruleus, and it is known to be present in the noradrenergic and histaminergic tracts. In the DH, GAL is found in intrinsic DH neurons. A consensus appears to exist that GAL is antinociceptive whereby it facilitates the DI of the NA and 5-HT pathways, but its role is dependent on the site of stimulus and presence of GAL receptor subtype as well as location of action (PNA, PNs, etc.). GAL is also thought to be released from NA cells themselves whereby it may be involved in negative feedback of NA neurons through autoreceptors on terminals from cells of the locus coeruleus.

Pools of nitric oxide (NO) are found throughout the CNS and are significantly involved in nociception at a variety of sites. Whether NO arises from descending sources or from local neurons in the DH, it appears to be a mediator of DF in the presence of inflammation or tissue injury. The action of NO may be through the facilitation of glutamate or through attenuation of DI systems at the DH. Similarly, NO may influence nociception through influence of NMDA pro-nociception or interruption of central DI mechanisms.

Lastly, cannabinoids are species of significant interest both scientifically as well as politically. Endogenous ligands to cannabinoid receptors CB-1 and CB-2 arise from membrane phospholipids. CB-1 is predominantly found in the CNS while CB-2 within the immune system. In fact, receptors for cannabinoids are found at nearly every level of the pain pathway. There is substantial support for the strong mechanism of antinociception not only supraspinally but also segmentally and peripherally in the presence of peripheral inflammation and neuropathic pain. Agonist studies demonstrate that peripheral sensitization is reduced with local administration in the hind paw rodent model, and antagonists block this response. Spinal mechanisms are mediated by CB receptors synthesized in the DRG and distributed to both axon terminals and dendrites. Activation of CB receptors may suppress local pro-nociceptive NTs in the DH or interfere with nociceptive transmission in PNs. Similarly, cannabinoids are thought to reduce the receptor fields of WDR neurons in the presence of persistent input. Supraspinal CB receptors are found in the PAG although these receptors are in anatomically different areas than the corresponding opioids, and this underscores their pathways as independent of the opioid-mediated pathways. Other sites of action involve the RVM whereby CB receptor-mediated activation of DI may occur. The influence of DI by cannabinoids appears to be particular to the NA pathway and less associated by mechanisms involving 5-HT receptors.

Key Points

1. Peripheral nociceptive afferent neurons target cells within the spinal cord that can lead to a significantly broad response in the central nervous system, and this is dependent on the tissue type, neurotransmitters, receptors, and second messenger systems involved.
2. The organization and function of afferent nociceptive transmission is dynamic and multimodal and is determined by the physiological or pathological circumstances present.

3. Independent nociceptive ascending tracts are an oversimplification, and the intercommunication between various ascending tracts is an important part of understanding the processing of pathological pain states.
4. The overall experience of pain is determined by the interaction between the two categories of ascending pathways, the sensory-discriminative and affective-cognitive.
5. The thalamus contains several nuclei that receive peripheral nociception and disperse it to a variety of higher centers involved in both the cognitive and subconscious response to pain. Dysfunction of innate inhibitory mechanisms within these higher centers may lead to pathological, unopposed pro-nociception.
6. Determinants of descending inhibition or descending facilitation are influenced by neurotransmitter concentrations and receptor subtype activation.
7. Descending modulation of nociception is complex and is dependent on a variety of mediators, some of which yet to be understood. Known mechanisms such as the noradrenergic and serotonergic pathways may have dual functions and are dependent on normal physiologic or pathological conditions in the periphery as well as supraspinal influences. Stimulus parameters and emotional-cognitive states strongly influence outcomes.

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